REMARKS

At page 18 of the Response filed on July 9, 2003, Applicants indicated that they are currently in the process of preparing a Declaration Under 37 CFR 1.132 in order to provide evidence of the absence of the 1793 dalton biopolymer marker(SEQ ID NO:1) in normal (non-diseased) human sera and will forward this Declaration to the Examiner as soon as it is complete. Applicants also indicated that they will further address the second rejection under U.S.C. 112, first paragraph at the time the Declaration is submitted.

The Declaration Under 37 CFR 1.132 is now complete and is submitted herewith. The second rejection under 35 USC 112, first paragraph presented in the Office Action mailed on April 7, 2003 is addressed below.

Rejection under 35 USC 112, first paragraph

Claims 3-9, 18-28 and 33-35, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which with it is most nearly connected, to make and/or use the invention.

The Examiner asserts that claims 3-9, 18-28 and 33-35 are broadly drawn to methods of determining the presence or absence of at least one disease state (specification only sets forth

congestive heart failure) by analyzing a biological sample obtained from a patient to identify the biopolymer marker sequence consisting of SEQ ID NO:1. The Examiner also asserts that the specification contemplates the use of these methods for diagnosing, staging, monitoring, prognosticating and determining predisposition to at least one disease state(specification only sets forth congestive heart failure).

Claims 3-9, 18-28 and 33-35 have been canceled. The remaining pending claims are now limited to methods and kits using a specific biopolymer marker peptide (SEQ ID NO:1) specifically diagnostic for congestive heart failure. The diagnostic methods of the remaining pending claims determine that the presence of SEQ ID NO:1 identified in a biological sample (bodily fluid or tissue sample) obtained from a patient is a positive indicator of congestive heart failure. The kits of the remaining pending claims are used to carry out the claimed specific diagnostic methods for congestive heart failure. Applicants respectfully draw the Examiner's attention to the fact that methods and/or kits involving staging, monitoring, prognosticating, determining predisposition to, evidencing, characterization and regulating at least one disease state are not claimed in the instant invention. Additionally, methods and/or kits involving risk-assessment, therapy and therapeutic identification as related to at least one disease state are not claimed. Applicants are not required to enable material that is not claimed

(see MPEP 2164.08).

The Examiner further asserts that it is not clear how the biopolymer marker will be utilized to distinguish any disease state, other than congestive heart failure because no other disease states were analyzed with the marker as a positive indicator of such disease state. In other words how will one identify any other disease state with the biopolymer marker having SEQ ID NO:1 when no such data has been presented. The Examiner asserts that the specification does not enable one of ordinary skill in the art to definitively assess the incidence or further distinguish between any and all disease states other than congestive heart failure. Applicants do not claim the ability to assess the incidence of a disease state, nor are Applicants claiming the ability to distinguish between any disease state. Further, Applicants do not claim that the biopolymer marker peptide consisting of SEQ ID NO:1 can identify disease states other than congestive heart failure. As is stated above, Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The instant inventors do not attempt to develop a reference "normal", but rather strive to specify particular markers which are evidentiary of at least one particular disease state, whereby the presence of said marker serves as a positive indicator of disease (see page 5, lines 7-11 of the instant specification). The presence of the claimed biopolymer marker peptide is a positive indicator

of myocardial infarction.

Applicants assert that the instant specification teaches those of skill in the art how the claimed peptide was isolated and identified without undue experimentation and further assert that the instant specification sets forth a protocol which can be followed to isolate and identify biopolymer markers of any disease condition. Pages 20-27 of the instant specification provide specific steps and protocols one would carry out to identify the claimed biopolymer marker peptide. Furthermore, the chromatographic and mass spectrometric techniques used in the protocols of the instant invention are well-known to those of skill in the art, thus it is not necessary to include every detail of the described protocols. Applicant is not required to describe what is well-known in the art. A patent need not teach, and preferably omits, what is well-known in the art (see MPEP 2164.01).

According to the methods of the instant invention; a biological sample(Page 28,line 11 to page 29,line 7 refers to the use of various types of samples and their measurement) is obtained from a patient(figure 1 shows data derived form patients) and first treated with one of the chromatographic protocols described on pages 20-25. The sample is then subjected to treatment with mass spectrometric techniques in order to identify the peptides present within the sample. The resulting spectral profiles of the peptides present in the sample are compared to spectral profiles of known

peptides. The peptides within the sample are further verified by comparison of their sequences to known sequences recorded in databases. One of skill in the art would recognize that the method described in the instant paragraph can be followed to identify biopolymer markers of any disease condition.

However, the Examiner asserts that the results obtained from the method which are set forth in figure 1, are not clearly indicative of at least one disease state because no control sample analysis is presented by way of example.

In response to this assertion, Applicants herein provide the attached Declaration (including one figure) under 37 CFR 1.132. The figure attached to the declaration provides side-by-side profiles (obtained using techniques of mass spectrometry) of healthy (normal) human sera versus sera from patients having a history of congestive heart failure. This profile comparison clearly evidences the absence of the 1793 dalton marker in normal human sera and thus establishes the specificity of the 1793 dalton peptide as a marker which when present in the sera is diagnostic for congestive heart failure. This figure does not represent results obtained from additional experimentation. The profiles were reproduced from data obtained in the original experiments performed at the time of the invention.

The Examiner further asserts that while the evidence presented in the specification does point to the high occurrence of the

sequence in congestive heart failure, this is not sufficient in implementing the said sequence in a molecular based diagnostic method for congestive heart failure and any other disease with said sequence. Applicants claim that the presence of SEQ ID NO:1 in the sera of a patient is indicative of congestive heart failure and enable this claim both by description of the procedures used to isolate and identify SEQ ID NO:1 in the specification and by example in the data shown in Figure 1. Applicants respectfully assert that this is enough to enable the claimed marker for diagnostic purpose in congestive heart failure.

The Examiner additionally asserts that Applicants have not provided any disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said sequence. Applicants have not claimed the ability to regulate the presence or absence of SEQ ID NO:1; Applicants observe the presence of SEQ ID NO:1 in biological samples obtained from patients. Furthermore, as stated above, Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The Examiner states that there is no disclosure designating how the sequence bound in the method that could be regarded as enabling one of ordinary skill in the art to use the said sequences in the diagnostic method. Applicants have shown by the description of methods set forth in the specification and exemplified by data in Figure 1 that the presence of SEQ ID NO:1 is a positive

indicator of congestive heart failure. Applicants respectfully submit that one of ordinary skill in the art after reviewing the specification and the declaration filed herewith would know how to use the claimed biopolymer marker peptide (SEQ ID NO:1) to diagnose congestive heart failure.

The Examiner cites two articles; Tascilar *et al.* (Annals of Oncology 10, Supplement 4:S107-S110 1999) and Tockman *et al.* (Cancer Research 52:2711s-2718s 1992) which are allegedly relevant to the instant invention. The Examiner did not provide a copy of the article by Tascilar *et al.* with the Office Action mailed on April 7, 2003, thus the article will be addressed in this response only with reference to what is written in the Office Action about the article.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods of the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently". Although it is difficult to clearly ascertain intended meaning from fragmented quotations presented out of context, the Examiner

appears to be commenting on the predictability of molecular-based assays. Applicants claim that the presence of SEQ ID NO:1 is a positive indicator of congestive heart failure; a statement which is enabled by the description of methods as set forth in the specification and by data presented in Figure 1. Thus, applicants respectfully submit that the claimed method involves a simple observation of the presence of SEQ ID NO:1 (as shown in Figure 1) and does not require any other evaluation of genetic changes in the organism in which the sequence is observed. Thus, it is respectfully submitted that the Tascilar *et al.* article is not relevant to the instant invention.

Tockman *et al.* is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al.* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al.* is deemed to teach that the

essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

The first thing noted about the Tockman *et al.* reference is the publication date; it was published almost ten years prior to the date of Applicants' invention. Theories and standards in biotechnology change quickly over time and especially over a decade. Thus, the Tockman *et al.* reference is not considered to accurately assess the field of the invention at the time of Applicants' invention.

The Tockman *et al.* article is concerned with early detection of cancer biomarkers and apparently does not discuss biomarkers for congestive heart failure. Although both the Tockman *et al.* reference and the instant invention are drawn to the identification of biomarkers, they are not considered to be analogous since a direct parallel can not be drawn between the neoplastic disease process and the disease process of congestive heart failure. The Tockman *et al.* is further not analogous in the type of markers taught. Tockman *et al.* discusses biomarkers for early detection of disease wherein in order to a show a marker for early detection the marker must be present before standard clinical diagnosis of the disease. Applicants identify the claimed biomarker (SEQ ID NO:1) in the serum of patients with a history of congestive heart

failure. Applicants are not claiming the marker to be present before the development of congestive heart failure, thus it is not necessary to link or validate the marker with confirmation of disease.

Furthermore, Applicants do not claim the marker to have any predictive value, thus there is no need to confirm marker predictive value in population trials.

Based on the considerations noted in the above paragraphs, it is respectfully submitted that the Tockman *et al.* article is not relevant to the instant invention.

Accordingly, as demonstrated in the above-discussion, Applicants assert that one of ordinary skill in the art when reviewing the instant specification and declaration filed herewith would recognize how to use the claimed peptide as a marker for congestive heart failure. Thus, Applicants respectfully request that this rejection under 35 U.S.C. 112, first paragraph now be withdrawn.

CONCLUSION

In light of the Response filed on July 9, 2003 and the remarks and Declaration Under 37 CFR 1. 132 submitted herewith, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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